congenital central hypoventilation syndrome

Congenital central hypoventilation syndrome (CCHS) is a disorder that affects breathing. People with this disorder take shallow breaths (hypoventilate), especially during sleep, resulting in a shortage of oxygen and a buildup of carbon dioxide in the blood. Ordinarily, the part of the nervous system that controls involuntary body processes (autonomic nervous system) would react to such an imbalance by stimulating the individual to breathe more deeply or wake up. This reaction is impaired in people with CCHS, and they must be supported with a machine to help them breathe (mechanical ventilation) or a device that stimulates a normal breathing pattern (diaphragm pacemaker). Some affected individuals need this support 24 hours a day, while others need it only at night.

Symptoms of CCHS usually become apparent shortly after birth. Affected infants hypoventilate upon falling asleep and exhibit a bluish appearance of the skin or lips (cyanosis). Cyanosis is caused by lack of oxygen in the blood. In some milder cases, CCHS may be diagnosed later in life. In addition to the breathing problem, people with this disorder may have difficulty regulating their heart rate and blood pressure, for example in response to exercise or changes in body position. They may have abnormalities in the nerves that control the digestive tract (Hirschsprung disease), resulting in severe constipation, intestinal blockage, and enlargement of the colon. They are also at increased risk of developing certain tumors of the nervous system called neuroblastomas, ganglioneuromas, and ganglioneuroblastomas. Some affected individuals develop learning difficulties or other neurological problems, which may be worsened by oxygen deprivation if treatment to support their breathing is not completely effective.

Individuals with CCHS usually have eye abnormalities, including a decreased response of the pupils to light. They also have decreased perception of pain, low body temperature, and occasional episodes of profuse sweating.

People with CCHS, especially children, may have a characteristic appearance with a short, wide, somewhat flattened face often described as "box-shaped." Life expectancy and the extent of any cognitive disabilities depend on the severity of the disorder, timing of the diagnosis, and the success of treatment.

Frequency

CCHS is a relatively rare disorder. Approximately 1,000 individuals with this condition have been identified. Researchers believe that some cases of sudden infant death syndrome (SIDS) or sudden unexplained death in children may be caused by undiagnosed CCHS.

Genetic Changes

Mutations in the *PHOX2B* gene cause CCHS. The *PHOX2B* gene provides instructions for making a protein that acts early in development to help promote the formation of nerve cells (neurons) and regulate the process by which the neurons mature to carry out specific functions (differentiation). The protein is active in the neural crest, which is a group of cells in the early embryo that give rise to many tissues and organs. Neural crest cells migrate to form parts of the autonomic nervous system, many tissues in the face and skull, and other tissue and cell types.

Mutations are believed to interfere with the PHOX2B protein's role in promoting neuron formation and differentiation, especially in the autonomic nervous system, resulting in the problems regulating breathing and other body functions that occur in CCHS.

Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

More than 90 percent of cases of CCHS result from new mutations in the *PHOX2B* gene. These cases occur in people with no history of the disorder in their family. Occasionally an affected person inherits the mutation from one affected parent. The number of such cases has been increasing as better treatment has allowed more affected individuals to live into adulthood.

About 5 to 10 percent of affected individuals inherit the mutation from a seemingly unaffected parent with somatic mosaicism. Somatic mosaicism means that some of the body's cells have a *PHOX2B* gene mutation, and others do not. A parent with mosaicism for a *PHOX2B* gene mutation may not show any signs or symptoms of CCHS.

Other Names for This Condition

- CCHS
- congenital central hypoventilation
- congenital failure of autonomic control
- Haddad syndrome
- Ondine-Hirschsprung disease
- Ondine Syndrome

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Congenital central hypoventilation https://www.ncbi.nlm.nih.gov/gtr/conditions/C1275808/

Other Diagnosis and Management Resources

- GeneReview: Congenital Central Hypoventilation Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1427
- MedlinePlus Encyclopedia: Hirschsprung's Disease
  https://medlineplus.gov/ency/article/001140.htm

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Hirschsprung's Disease
  https://medlineplus.gov/ency/article/001140.htm
- Health Topic: Autonomic Nervous System Disorders
  https://medlineplus.gov/autonomicnervoussystemdisorders.html

Genetic and Rare Diseases Information Center

- Congenital central hypoventilation syndrome
  https://rarediseases.info.nih.gov/diseases/8535/congenital-central-hypoventilation-syndrome

Educational Resources

- American Academy of Sleep Medicine
  http://www.sleepeducation.org/sleep-disorders-by-category/sleep-breathing-disorders/central-sleep-apnea/overview-facts/
- Disease InfoSearch: Congenital Central Hypoventilation Syndrome
  http://www.diseaseinfosearch.org/Congenital+Central+Hypoventilation+Syndrome/1794

- My46 Trait Profile
  https://www.my46.org/trait-document?trait=Congenital%20central%20hypoventilation%20syndrome&type=profile
- Orphanet: Ondine syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=661

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/congenital-central-hypoventilation-syndrome/

GeneReviews

- Congenital Central Hypoventilation Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1427

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22congenital+central+hypoventilation+syndrome%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Sleep+Apnea,+Central%5BMAJR%5D%29+AND+%28congenital+central+hypoventilation+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- CENTRAL HYPOVENTILATION SYNDROME, CONGENITAL
  http://omim.org/entry/209880

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